Review Article

Current Trends in Ophthalmology

Adjunctive Antifibrotic Therapy with Mitomycin C and 5-Fluorouracil: A Review of their use in Glaucoma Surgery and Considerations around Ophthalmic Compounding

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Abstract

Background: Antifibrotics and antimetabolites, including 5-fluorouracil (5-FU) and mitomycin C (MMC), have been used for decades to improve ophthalmic surgical outcomes, most notably with glaucoma filtering procedures. Adjuvant MMC and 5-FU also enhance the efficacy of minimally invasive subconjunctival drainage implants now being used. The authors feel that a review of the usage and safety of these agents is merited, especially in light of updated and new USP guidelines for compounded and hazardous drugs.

Main Body: The mode of perioperative administration of MMC during glaucoma surgery is evolving with a shift from the traditional sponge application to subconjunctival injection, allowing for a more precise dosing and controlled administration of this medication. Several studies demonstrate effective use of MMC and 5-FU, at a variety of different doses. Most of these studies use compounded MMC and 5-FU. Glaucoma surgeons must be careful in how they source MMC, however, as the U.S. Food & Drug Administration (FDA) expects physicians to use FDA-approved drug products when clinically appropriate. When a physician determines a compounded version of MMC is clinically necessary for an individual patient, the FDA closely regulates how and when drug products can be compounded and by what type of facilities. There will also be additional increased scrutiny on storage and disposal of MMC and 5-FU as new regulations are introduced.

Conclusion: This review of MMC and 5-FU and their role in glaucoma surgery will address questions regarding drug safety, procurement, use, and disposal.

Keywords: Compounding, Glaucoma, MIGS, Mitomycin C, 5-Fluorouracil

Abbreviations: 5-FU: 5-Fluorouracil; AAO: American Academy of Ophthalmology; ACHC: Pharmacy Compounding Accreditation Board; ASORN: American Society of Ophthalmic Nurses; cGMP: Current Good Manufacturing Processes; CMS: Centers of Medicare and Medicaid Services; CTSD: Closed-system Transfer Device; FDA: Food and Drug Administration; FD&C: Food Drug & Cosmetic Act; MMC: Mitomycin C; HCP: Healthcare Personnel; MIGS: Micro-invasive Glaucoma Surgery; NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration; PPE: Personal Protective Equipment; USP: United States Pharmacopeia

Introduction

Mitomycin C (MMC) and 5-Fluorouracil (5-FU) are well recognized chemotherapeutic agents widely used in oncology. In addition to their antineoplastic activity, these compounds also possess antifibrotic and antiproliferative properties [1-5]. Such properties are recognized as being beneficial in ophthalmic procedures, particularly in glaucoma filtering surgery, where these agents have been used since the 1980s to prevent premature closing of the surgically created sclerotomy and surrounding fibrosis [1-5]. Two micro invasive glaucoma surgery (MIGS) devices (the ab-interno XEN Gel Stent, Allergan, and the ab-externo MicroShunt, InnFocus/Santen) are bleb-based procedures that result in subconjunctival filtration blebs for ongoing pressure reduction [6]. These procedures also benefit from the intraoperative use of MMC and 5-FU as a means to prevent episcleral fibrosis. As such, it is worthwhile to review the literature on safety and dosing, as well as become familiar with the new and updated regulations surrounding their use.

History of use of MMC and 5-fu in ophthalmic surgery

MMC reduces collagen synthesis and proliferation and can induce apoptosis, which contributes to its success in ophthalmic surgeries [7-9]. MMC also affects nearly all profibrotic processes of conjunctival fibroblasts [10] and is cytotoxic to both fibroblasts and endothelial cells [5]. It is this ability to inhibit fibroblast proliferation that has led to the topical (and frequently off-label) use of MMC in a variety of ophthalmic surgeries. As explained below, when used in ophthalmic surgery, the concentration and exposure time are critical for finding an optimum pharmacologic effect of topical MMC. The FDA-approved MMC product Mitosol (Mitomycin solution 0.2 mg/vial), is commercially available in a single-use formulation and, is intended for topical application to the surgical site of glaucoma filtration surgery [6], but is also often used off-label in other ophthalmic surgeries.

Similarly, the role of 5-FU is to reduce fibroblast proliferation and subsequent scarring and it is often used off-label in ocular and periorbital surgeries [11].

The use of both 5-FU and MMC in ophthalmic surgery is well described in many ophthalmic studies [12-33]. The concentration and dose of MMC and 5-FU may vary and as a result, compounded versions of the two drugs were frequently used. MMC in particular is often extemporaneously prepared by a pharmacy or in-

house facility, and the literature has discussed various concentrations that are effective in ophthalmic surgery [24,26]. The FDA-approved MMC products have to be reconstituted from a powder and therefore the potential for various concentrations and dilutions using the FDA-approved products are, therefore, readily available. The FDA-approved 5-FU product is in solution and is a fixed concentration of 50 mg/mL. Therefore, the only concentrations available would require dilution of the FDA-approved product to a lower concentration.

MMC is often used off-label during refractive surgery to prophylactically decrease haze after surface ablation procedures with numerous results reported in the literature [22-26,34]. At this time, AAO has stated the "optimal dosage, effectiveness as prophylaxis in lower myopic and hyperopic ablations, and long-term safety, particularly in eyes with reduced corneal endothelial cell counts from prior intraocular surgery, have yet to be established" [12].

MMC is also commonly used during pterygium surgery (also an off-label use), and several reports in the literature suggest use can reduce pterygium recurrence rates [16,19,20,33]. As with refractive surgery, there is no gold standard concentration used and the dosage and routes of MMC administration may vary.

MMC is widely used in glaucoma filtration surgery to prevent scarring in the subconjunctival space [31] and it is now approved by FDA for use as an adjunct [23,35] for application with a topical sponge. Its use in conjunctival neoplasm's is secondary to glaucoma filtration [36], and efficacy is highly associated with concentration and application time used [37,38], as well as patient and surgical variables [39]. 5-FU administration post trabeculectomy was used more when antimetabolites were initially studied in glaucoma filtration surgery. However, over the years the single application of MMC is associated with a more potent antifibrotic effect than 5-FU and is used more frequently. Singh et al., compared 5-FU 50 mg/mL application for 5 minutes to MMC 0.4 mg/ml by sponge application for 2 minutes as adjuncts with primary trabeculectomy and found them equally safe and effective in both the short and midterm postoperative periods [40].

Use of MMC and 5-fu in glaucoma surgery

How ophthalmic surgeons administer MMC in glaucoma procedures is still undergoing evolution and varies depending upon route of administration and the

concentrations utilized.

Perioperative administration of MMC is evolving with a shift from the traditional sponge application to a subconjunctival injection allowing for a more precise dosing and controlled administration. Pakravan et al. [41] found a sub-Tenon injection of 0.1 mL of 0.01% MMC produced more favorable bleb morphology after trabeculectomy than 0.02% MMC-soaked sponges placed under Tenon's and subconjunctivally over the scleral flap for 1 or 3 minutes, with the time of sponge placement determined by the surgeon. Khouri et al. [42] concluded that injecting MMC was as safe and effective as the applications by sponge with comparable treatment success, involved fewer visits within 3 months and fewer postoperative 5-FU interventions than traditional sponge applications. Esfandiari et al. [43] recently reported on 3-year outcomes of trabeculectomy with MMC 0.02% soaked sponges versus 0.1 ml of 0.01% intra-Tenon MMC injection. Both were found comparable in success rate and IOP reduction, although bleb morphologic parameters favored intra-Tenon MMC injection [43].

Two authors (RN and AS) have found a volume of injection of 0.1-0.2 ml is typically sufficient to provide a zone of exposure wide enough to create a low, diffuse filtration area subconjunctivally in an eye without significant scarring risk (e.g. a very young patient with prior failed glaucoma surgeries) (Videos 1 and 2). They may also use 5-FU 0.1 ml for a total of a 5-mg dose. They recognize there is diffusion of the MMC beyond the area of initial injection and larger volumes may create limbal blebs that may be cosmetically undesirable. Anecdotally, a smaller volume of a higher concentration of MMC may result in a smaller localized bleb that is more prone to thinning and fibrosis.

Video 1: Injection of MMC following XEN Gel Stent Placement.

Video 2: Technique for posterior placement of MMC

With the XEN Gel Stent, MMC can be delivered by a sponge directly to the sclera or by subconjunctival injection [44,45]. The majority of the XEN studies have utilized subconjunctival infiltration of MMC. The subconjunctival space is accessed surgically in studies on the MicroShunt, allowing MMC to be delivered topically [46]. Others have reported on the use of MMC via injection, but again with different techniques. Galel et al. [47] chose to inject 0.1 mL MMC 0.01% under Tenon's and spread with a micro sponge applied to the conjunctiva in the superior nasal quadrant. Schlenker et al. [45] evaluated 185 eyes injected with 0.05 to 0.2 ml MMC 0.2 mg/ml 20 minutes before surgery in the superonasal quadrant or superotemporal quadrant and massaged over the area of anticipated microstent insertion. Mansouri et al. [48] used intraoperative 0.1 ml MMC 0.02% injected subconjunctivally via a 27-gauge hypodermic needle under Tenon's capsule and spread with a micro sponge applied to conjunctiva in the superior nasal quadrant where the implant would be inserted, where it remained for 10 minutes before the implant was injected.

There are no universal concentrations for injected MMC that have emerged yet as a "gold standard" during subconjunctival MIGS surgery. Anecdotal reports [49] include 0.4 mg/cc of MMC 10 to 12 mm posterior to the limbus with a 30-gauge needle, to 0.2 ml of a 50/50 mixture of 1% MPF lidocaine and 0.2 mg/mL MMC into the superior subconjunctival space, to 0.1 cc of 0.2 mg/ml MMC injected around 6.0 mm behind the limbus with a Weck-cel sponge used to keep fluid from the limbus, to 0.2 mg/cc injecting just under 0.1 cc. Two authors (RN and AS) prefer to inject MMC after XEN implantation to ensure a specific volume is delivered; both authors recommend

injecting away from the limbus. Unpublished data from one author (AS) suggests an off-label use where Mitosol is concentrated from the manufactured 0.2 mg/ml to 0.4 mg/ml.; the author then injects 0.1 to 0.2 ml typically unless the patient is at a very high risk for scarring. For a patient at high risk for scarring, he would recommend surgeons inject 60 to 80 mcg of MMC and consider needling the bleb in the operating room at the time of implantation to ensure the XEN is free from tenon's tissue. Another author (RN) uses a concentration of compounded MMC of 0.2 mg/cc. which is then diluted with 2% lidocaine to provide anesthesia as well. A total volume of 0.2 cc of the mixture is then injected with a 30-gauge needle superiorly far away from the limbus allowing space for the MMC to travel forward to the limbus, but localized to the area underneath the upper eyelid.

Others also have recommended MMC at a concentration of 0.1 to 0.2 mg/mL (at a total volume of 0.1 mL for an absolute dose range of 10 to 20 µg), which is a lower concentration than is typically used during trabeculectomy [50]. Should bleb needling be necessary, reports suggest the adjunctive use of MMC can be helpful, with a dose that ranges from 0.1 mg/mL to 0.4 mg/mL in a total volume of 0.1 mL [51]. A recent study after XEN implantation with adjunctive MMC employed a needling revision with 0.2 mL of 5-FU (2.5% or 5 mg) [51]. Patients exhibited a good IOP lowering effect without a significant increase in anti-glaucoma medication use or major complications.

The safety profile of MMC and 5-fu in glaucoma surgeries

There have not been any reports of systemic complications caused by the ocular use of MMC, and it is unlikely considering the low quantities of MMC used in filtration procedures [52]. However, a recent study of subconjunctival MMC in XEN implantation found similar IOP lowering, glaucoma medication reduction and self-limiting and self-resolving hypotony as previous MMC sponge-administered trials for XEN with continued effectiveness out to 2 years [53].

Another important consideration is the use of a subconjunctival injection of MMC versus sponge application. Most studies have reviewed the older technique of topical sponge application of MMC and therefore the risk for subconjunctival MMC needs to be further studied. In a meta-analysis of compounded sponge application of MMC use in filtration surgery,

the relative risk for adverse events that included bleb leakage, hypotony, endophthalmitis, and shallow anterior chamber were not statistically significantly different between MMC and 5-FU [54]. Sponge application of MMC and 5-FU have been reported to create excessive collateral tissue damage and increase complications during the postoperative period [55]. A recent Cochrane Review on 5-FU use both during and after surgery found a small, but statistically significant, reduction in surgical failures and IOP intraocular pressure 1 year after primary trabeculectomy but cautioned those advantages should be weighed against the increased risk of complications and patient preferences [56]. A separate Cochrane Review found trial participants who received antimetabolites by varied methodology of application, that MMC to have more reported bleb leaks, wound leaks, late hypotony, and cataract formation than those who received 5-FU, but cautioned the quality of evidence was low given the rarity of adverse events [4].

The use of sponge-soaked MMC has been cited to result in increased risk of wound/bleb leaks, hypotony, cataracts, or hypotony maculopathy [57,58]. On the other hand, a 9-year follow-up of patients who underwent trabeculectomy with or without MMC found no differences in leaks, hypotony, blebitis, or endophthalmitis [59]. In the MMC topical sponge application arm of the Tube Versus Trabeculectomy Study (TVT Study), there was a low cumulative incidence of bleb leaks (6%), hypotony maculopathy (5%), and blebitis/endophthalmitis (5%) [60,61] at 5 years. Tube shunt surgery patients had a cumulative probability of failure of 29.8% versus 46.9% in the trabeculectomy group at the 5 year follow up. With 4 years of follow-up, a comparison of outcomes between trabeculectomy augmented with either MMC or 5-FU found bleb leakage was the most common complication, developing in about 4% of patients each year [62]. Future studies need to be performed to determine the incidence of similar side effects with injected MMC. Esfandiari et al. [43] found no difference between sub-tenon MMC injections versus sponge soaked MMC at 3 years regarding complication rates and endothelial cell count in trabeculectomy patients.

There are inherent risks in using compounded drugs, particularly drug products that must be sterile. As FDA has repeatedly cautioned physicians, compounded drugs "pose higher risks to patients than FDA-approved drugs. Compounded drugs are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality". FDA has further

cautioned that “[t]here can be health risks associated with compounded drugs that do not meet federal quality standards. Compounded drugs made using poor quality practices may be sub- or super-potent, contaminated, or otherwise adulterated”. The risks associated with compounding drugs that must be sterile are particularly relevant in the ophthalmic space. For example, on July 28, 2017, FDA announced that it had received adverse event reports for at least 43 patients who had intravitreal (eye) injections of a compounded mixture of triamcinolone and moxifloxacin during cataract surgery. The adverse events included blurred and decreased vision. On October 3, 2017, FDA announced that it had received adverse event reports (i.e., hemorrhagic occlusive retinal vasculitis) for dozens of patients who had eye injections of a compounded drug containing vancomycin during cataract surgery.

Fortunately, the risks associated with compounding MMC can be decreased (although not eliminated entirely) by compounding from an FDA-approved drug product rather than a bulk drug substance. As noted above, FDA has made it very clear that compounding using bulk drug substances presents a greater risk than compounding using FDA-approved drug products. Here, the FDA-approved versions of MMC would meet patients’ medical needs and compounding using them (rather than using bulk drug substances) would therefore present less risk. Indeed, FDA specifically cites the dilution of an FDA-approved drug product as an example of a less risky form of compounding.

Availability of MMC and 5-fu in the United States

There are several versions of MMC approved by the U.S. Food and Drug Administration (FDA). Mitosol (Mobius Therapeutics, USA) is a sterile lyophilized mixture of 0.2 mg MMC and 0.4 mg Mannitol, which when reconstituted with Sterile Water for Injection provides a solution for topical administration [6]. Mitosol is approved for topical ophthalmic use via a sponge application and is not approved for injecting subconjunctivally.

Mitomycin (Accord Biopharma, USA) is approved as an intravenous chemotherapy agent [63]. Mitomycin is a sterile dry mixture of MMC and mannitol, which when reconstituted with Sterile Water for Injection provides a solution for intravenous administration. Each vial of Mitomycin contains either 5 mg of MMC (and 10 mg of mannitol), 20 mg of MMC (and 40 mg of mannitol), or 40 mg of MMC (and 80 mg of mannitol). Mitomycin is not

approved for ophthalmic use. Mylan Labs and West-Ward Pharmaceuticals market generic versions as well.

5-FU injection is as antineoplastic antimetabolites that are available from multiple manufacturers in a generic version. 5-FU is a sterile, nonpyrogenic injectable solution for intravenous administration containing in 1 mL 50 mg fluorouracil. Each 1 mL contains 50 mg fluorouracil and the pH is adjusted to approximately 9.2 with sodium hydroxide. For intravenous use fluorouracil injection is available in various size vials.

Because MMC sponge application may not be clinically appropriate, or because the FDA-approved strengths of MMC may not be clinically appropriate, ophthalmologists are often unable to use name brand or generic versions of MMC during certain glaucoma surgeries. The ophthalmic use of 5-FU is also limited by the same constraints because there is no FDA approved product for topical and subconjunctival administration. In such situations, ophthalmologists seek out compounded versions of MMC and 5-FU through their own pharmacy or elsewhere.

FDA Regulation of compounding

The use of compounded drugs in the ophthalmic space, however, raises a number of concerns. The FDA and State Boards of Pharmacy closely regulate the practice of pharmacy compounding. In addition to sterile compounding regulations, MMC and 5-FU are also classified as hazardous drugs by the National Institute of Occupational Safety (NIOSH) chemotherapeutic agents. Administration of these compounds also requires adherence to additional considerations around hazardous drug procurement and disposal.

The FDA expects the physicians to prescribe and administer FDA-approved drugs whenever they are commercially available because such drugs are subject to FDA’s rigorous premarket review for safety, effectiveness, and quality. In addition, they are also manufactured by a facility that is subject to premarket assessment, including site inspection, pursuant to FDA’s stringent current good manufacturing practices (cGMP) regulations. The Agency recognizes, however, that in certain situations it may be necessary to modify a commercially available drug product in order to provide a clinically meaningful difference to an individual patient. In such cases, FDA acknowledges the necessity of drug compounding. FDA regulates drug compounding under Sections 503A and 503B of the Food Drug & Cosmetic Act (FD&C Act) [21,22].

Under Section 503A of the FD&C Act, a pharmacy may engage in traditional pharmacy compounding provided that it (1) limits its compounding to prescriptions for identified individual patients and makes no more than limited quantities of compounded drugs in advance of receiving prescriptions, (2) does not make drugs (either regularly or in inordinate amounts) that are essentially copies of commercially available drugs, and (3) uses permissible ingredients. It is important to highlight that the higher rigors of cGMP regulations for manufacturing are not evident in most compounding pharmacies. Permissible ingredients according to the FDA, states that pharmacies should, absent a demonstrated clinical need, compound from the FDA-approved product rather than from bulk ingredients. Products prepared by traditional pharmacy compounders must also not be contaminated or prepared under insanitary conditions, must be the correct strength and purity, and the drugs' labeling, advertising, and promotion must not be false or misleading.

Under Section 503B of the FD&C Act, so-called "outsourcing facilities" may compound drugs in unlimited quantities (without first receiving prescriptions) if they are compounding drugs for which there is a drug shortage or compounding drugs using specific ingredients, as identified on a list published by FDA, for which there is a clinical need. Note, however, that FDA has further explained that the source, safety, and quality of the starting material are better known and established when an FDA-approved drug product is used instead of bulk drug substance for compounding. As a result, if a drug product can be compounded from an FDA-approved drug, the Agency has taken the position that there is no clinical need for an outsourcing facility to compound the drug from a bulk substance. In addition, outsourcing facilities, similar to traditional pharmacy compounders operating under Section 503A, cannot compound drugs that are essentially a copy of one or more approved drugs. Outsourcing facilities must also, among other things: (1) comply with FDA's stringent cGMP regulations; (2) open its operations to FDA inspections; (3) report adverse events to FDA; and (4) provide FDA with detailed information about the products they compound. Registration of 503B facilities with FDA is a voluntary requirement.

Unified classification of hazardous drugs

Like FDA, the United States Pharmacopeia (USP) notes that pharmaceutical compounding "provides access to medication for patients who may not be able to use commercially available formulations due to dosing

requirements, allergies or rare diseases" [64]. While outsourcing facilities operating under Section 503B of the FD&C Act must follow FDA's cGMP regulations, FDA requires pharmacies compounding under Section 503A of the FD&C Act to follow Chapter <797> of the USP and all referenced USP chapters within the chapter. USP Chapter <797> is devoted to pharmaceutical compounding for sterile preparations; an update was released on July 31, 2018, with a public comment period from September 4 to November 30, 2018. The purpose of the Chapter <797> standards is to reduce the potential for infection and harm that can be caused by compounded sterile pharmaceutical products. These guidelines are enforceable by state boards of pharmacy and may also be enforced by FDA under §§501 and 502 of the Federal Food, Drug and Cosmetics Act [24].

USP Chapter <800>, "Hazardous Drug- Handling in the Health Care Settings" is in final form with an expected date of compliance of December 1, 2019. This chapter is designated to protect healthcare providers and patients. According to the International Agency for Research on Cancer, MMC is considered a Group 2B possible carcinogen [34,65] and is further classified by Department of Health and Human Services, Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (NIOSH) as Health Hazard Group 1 Antineoplastic Hazardous Drug [66]. NIOSH also notes that Group 1 designated drugs "represent an occupational hazard to healthcare workers and should always be handled with use of recommended engineering controls and personal protective equipment (PPE), regardless of their formulation" [66]. MMC is designated as an FDA pregnancy-risk Category D and exposure to MMC by a pregnant healthcare provider should be considered hazardous [66].

A recent report from the American Academy of Ophthalmology (AAO) noted that MMC must be reconstituted from its powder form by a pharmacy or by trained personnel, but noted its carcinogenic categorization requires special handling and imprecise dilution can lead to significant ocular morbidity [12].

A similar warning is also used with 5-FU [13]. With 5-FU, the risk to healthcare professionals resides in reproductive risk and the compound is designated as an FDA pregnancy-risk Category D drug product; exposure to 5-FU by a pregnant healthcare provider should be considered hazardous. Because of this hazardous designation, 5-FU is also regulated under USP

Chapter <797> for preparation for patient safety and will be regulated under the new USP Chapter <800> for healthcare provider safety for handling.

To date, Mitosol is the only FDA approved agent for use in glaucoma filtration surgery [50]. Per the manufacturer, the Mitosol kit is comprised of 0.2 mg of lyophilized MMC powder, 1 mL of sterile water for injection, precut sponges, and all necessary components for contained preparation (including a Closed-System Transfer Device) and transfer along with safe disposal (<https://mobiustherapeutics.com/product/mitosol-kit/>).

Once reconstituted, the solution contains 0.2 mg/mL MMC [23,35]. As with all MMC products, health hazards are NIOSH Group 1 and NIOSH Group 3, with directions from the manufacturer to use, treat, and dispose of as hazardous drug waste [23]. While reconstituting MMC per the manufacturer's instructions in the FDA-approved package insert is not considered compounding by FDA, it is considered compounding per updated USP <797>. The USP <797> guidelines state that compounding is the process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication.

A traditional compounding pharmacy operating under Section 503A of the FD&C Act can produce about 25 doses of 0.4 mg/mL from a single 5-mg vial of the FDA-approved drug Mitomycin [21]. The process of drawing multiple individual doses out of a vial that is reconstituted is considered batching (a compounding process). If the expiration dating exceeds what is defined specifically within the FDA-approved package insert, the 503A pharmacy must follow standards outlined within USP <797> and conduct appropriate testing for sterility and stability of the final products for use. An outsourcing facility operating under Section 503B of the FD&C Act must comply with FDA's more stringent cGMP requirements.

Compounded MMC

Despite the availability of Mitosol, many glaucoma surgeons continue to use compounded MMC, typically sourced from in-house pharmacies or third-party vendors. As explained above, we would strongly caution glaucoma surgeons to only source compounded MMC when clinically necessary and then only from pharmacies lawfully operating under Section 503A of the FD&C Act or from third-party vendors that are registered with FDA as outsourcing facilities and are lawfully operating under Section 503B of the FD&C Act.

The concentrations of compounded MMC that glaucoma surgeons receive are typically between 0.2 and 0.4 mg/mL. We would note, however, that when Mitosol is reconstituted pursuant to the FDA-approved package insert, it becomes 0.2 mg/mL. As a result, in the absence of other clinical need(s), there is no legitimate reason to have that specific strength compounded. Indeed, even if the glaucoma surgeon plans on using the FDA-approved MMC for an off-label use, the surgeon should use the FDA-approved version of the MMC (rather than a compounded version) if a concentration of 0.2 mg/mL is clinically appropriate.

The various concentrations used by glaucoma surgeons are typically based on risk factors (previous surgery, age, and race/ethnicity) for postoperative complications that include scarring and over filtration [39]. The reasons for preferring a compounded version rather than the FDA-approved versions for ophthalmic surgery may be due to the use of different concentrations and suitability for procedures where conjunctival dissection is not required. The reasons for preferring a compounded version must, of course, be based on clinical need, so the fact that a compounded version of the drug may be less expensive than the FDA-approved version of the drug would not serve as an appropriate basis for using a compounded version of the drug. Future consideration based upon updated USP 797 and new USP 800 guidelines may also raise additional discussion.

The use of compounded MMC from different pharmacies may present some concerns around concentration accuracy. The FDA does not routinely review, approve or assess the safety of compounded sterile preparations at compounding pharmacies and, as noted above, FDA is very concerned about compounded drugs being safe for patient use and demonstrating, sterility, stability, without variations in either sub- or super-potency. The variability in methodology and concentrations may impact the quality of compounded MMC being used [21]. Kinast et al., evaluated 60 samples of 0.4 mg/mL of MMC that were stored in a variety of methods (including refrigeration, freezing, and immediately compounded dry powder) and from a variety of pharmacies (including an academic hospital, a community hospital, and an accredited independent compounding pharmacy) and compared MMC concentration to pure MMC. They stated, "common compounding and storage techniques for MMC resulted in a lower accuracy and wider range of concentration than expected" and found all samples on average were

12.5% lower in concentration than the expected 0.4 mg/mL, with a wide concentration range between 0.26 and 0.46 mg/mL [21]. Velpandian et al. [36] showed keeping MMC at lower temperatures and within a pH of 7 or 8 could significantly decrease degradation rates.

The potential for eye damage when using compounded pharmaceuticals is not unique to the glaucoma specialty. In addition to the more recent examples cited above, infectious and noninfectious endophthalmitis outbreaks were reported in 2011 after the use of compounded bevacizumab for intravitreal injection. It was determined that the subsequent vision loss was caused not by injection technique or efficacy of the drug, but by the compounding procedures used to prepare syringes [51]. Further, strict adherence to USP Chapter <797> requirements was recommended [51,67]. This led to the AAO recommending physicians to select a compounding pharmacy accredited by the Pharmacy Compounding Accreditation Board (ACHC, achc.org) that “adheres to quality standards for aseptic compounding of sterile medications” [68]. In addition to this recommendation, we

have included a number of additional recommendations in the sidebar.

Conclusion

The introduction of certain MIGS procedures that involve the subconjunctival space will potentially increase the use of MMC and 5-FU. This increases the need for surgeons to be aware of the safety, efficacy and safe handling of these drugs especially in light of updated and new USP regulations. To date, outbreaks from other compounded medications have not occurred with the use of MMC or 5-FU in glaucoma filtration surgery or in MIGS. It is the authors’ belief that careful attention to reconstituting Mitosol per the manufacturers’ instructions in the FDA-approved package insert or ensuring that MMC, if there is a clinical need for it to be compounded, is compounded from the FDA-approved MMC product (rather than from a bulk drug substance) in a facility lawfully operating under either Section 503A or 503B of the FD&C Act, will help ensure those types of outbreaks do not occur in glaucoma surgery.

Hazardous drug handling responsibilities

Regulations exist for sites to consider when handling hazardous drugs such as MMC and 5-FU. The Department of Labor’s Occupational Safety and Health Administration has provided employers with guidelines and responsibilities for educating and protecting personnel [69,70]. Employers must define occupational hazards for employees and must educate and employ protective measures. The National Institute of Occupational Safety and Health (a joint organization formed between the Centers for Disease Control and the Occupational Safety and Health Administration) assist sites by providing a published list of hazardous drugs every 2 years [66]. The drugs are stratified into three occupational hazards categories; Group 1 Antineoplastic Hazardous Drugs (both 5-FU and MMC are in this class of drugs); Group 2 Non-antineoplastic Hazardous Drugs; and Group 3 Non-antineoplastic drugs that primarily have adverse reproductive effects (MMC has this additional hazard classification). Of note, some drugs like MMC can have designation within two groups; Group 1 and Group 3 and may require additional protective measures.

The Centers for Medicare and Medicaid Services has designated the USP as the required standard for the compounding of drugs by a pharmacy operating under Section 503A of the FD&C Act and requires sites receiving reimbursement to assure compliance with USP standards for the products used on patients and billed to Centers of Medicare and Medicaid Services (CMS). Outsourcing facilities operating under Section 503B of the FD&C Act, however, are required to follow FDA’s more stringent cGMP requirements.

In USP <797>, the emphasis is on minimizing the risk of contaminating and adulteration of medicines when compounding sterile preparations [67]. USP <800> is primarily focused with protecting all healthcare workers, patients, and the general public who have access to any facility where hazardous drugs are stored, prepared and administered [71]. USP <800> standards rely upon USP <797> for the standards regarding sterile compounding for hazardous drugs, and the two chapters must be considered synonymously with MMC and 5-FU handling.

Defined within USP <800> are requirements for the use of specially designed personal protective equipment (e.g. two pairs of chemotherapy gloves ASTM D6978 rated), use of special engineering controls (e.g. biological

safety cabinets, closed-system drug transfer devices for compounding and administration of hazardous drugs), and facility requirements for the safe storage, compounding, and disposal for sterile and nonsterile antineoplastic hazardous drugs [71]. Compounding pharmacies that handle MMC and 5-FU must adhere to USP <797> for patient safety and must adhere to USP <800> for healthcare provider safety and FDA-registered outsourcing facilities must comply with an even more stringent set of standards. The Environmental Protection Agency has provided guidance on the proper disposal of hazardous drugs and the corresponding wastes, (e.g. residual MMC in syringes or vials and plegits), under the Resource, Conservation and Recovery Act, and sites must refer to state and federal regulations for their safe disposal [72].

How to safely source compounded MMC

When it is clinically necessary to use a compounded drug, the author recommendations (CL and FM) for sourcing compounded MMC include those issued by the AAO for sourcing bevacizumab for intravitreal injections [73].

The AAO recommended physicians select a compounding pharmacy licensed by a state board of pharmacy and accredited by the ACHC that “adheres to quality standards for aseptic compounding of sterile medications” [73].

Local pharmacies can be found on the ACHC site if the physician does not currently have access to an accredited compounding pharmacy. It is ultimately the responsibility of the physician, however, to vet the compounding facility to confirm that, even if accredited by ACHC, it is in compliance with the FD&C Act. To that end, the Authors further recommend that a physician should specifically ask the pharmacist in charge:

1. If the facility is operating under Section 503A or Section 503B of the FD&C Act [74-77]. A physician should be wary of a facility that claims it is not regulated by FDA or claims to be operating under Section 503A of the FD&C Act, yet is obviously not engaged in traditional pharmacy compounding, e.g., it is not universally asking for prescriptions for individually identified patients prior to dispensing drugs or is manufacturing in large quantities.
2. To confirm that the facility will compound the MMC and 5-FU from FDA-approved drugs rather than from bulk drug substances.
3. To confirm that the facility conducts tests to confirm both sterility and stability of the product for the assigned beyond use date.
4. To confirm the facility is licensed by a state authority (for facilities operating under Section 503A of the FD&C Act) or registered with the FDA (for facilities operating as outsourcing facilities under Section 503B of the FD&C Act). A physician can easily and quickly confirm that an outsourcing facility is registered with FDA simply by looking at the following website dedicated to actively listing all Registered Outsourcing Facilities: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>
5. To confirm that the facility is complying with chapter <797> of the USP (for facilities operating under Section 503A of the FD&C Act) or with the FDA’s cGMP regulations (for facilities operating as outsourcing facilities under Section 503B of the FD&C Act). To that end, a physician should specifically ask whether in the last five (5) years FDA has issued the facility a Form 483 (which describes violations of the FD&C Act found during an FDA inspection) and/or a warning letter. If so, the physician should carefully review these documents prior to placing any orders with the facility. (<https://www.fda.gov/iceci/inspections/ucm256377.htm>)
6. Whether a state regulatory authority has, within the last 5 years, issued the facility and/or its owners an inspection report, regulatory letter, or Cease and Desist order.
7. Whether the facility has had to recall compounded products within the last 5 years.

In addition, the business agreement between the physician and the pharmacist should require the compounding facility to provide the physician with real-time notification of any adverse events or recalls associated with compounded drug products. The business agreement should also require the facility to promptly share any communications between the facility and FDA and/or state regulators, including inspection reports and warning letters that relate to the safety, efficacy or quality of compounded drugs. The business agreement should also

include the facility's commitment to complying with all applicable federal and state requirements, along with all relevant USP chapters, including chapter <800>.

Document the facility's answers to the questions discussed above (along with your own assessment of the facility). Include any documentation that can be procured (such as Form 483s and warning letters) that shows whether the compounding facility is adherent to compounding standards (USP <797> for 503A facilities and cGMPs for 503B outsourcing facilities) and USP <800>, especially regarding personal protective equipment for its employees.

Become familiar with your state regulations. State-by-state regulations vary; some states mandate all pharmacies

register with the state and are recognized. Other states do not have those requirements and in some cases (i.e., Nebraska), "hospital pharmacy" is not a recognized profession although "retail pharmacy" is (i.e., California). The Centers for Medicaid and Medicare Services directed facilities to follow <797> Guidelines and corresponding chapter for sterile compounding; failure to do so may result in loss of funding for that facility. Physicians should review their state boards of pharmacy websites for statutory regulations regarding compounding drugs, outsourcing compounded products and requirements for outsourcing facilities. It is the ultimate responsibility of the healthcare provider ordering, preparing, and administering a drug to assure that it was prepared and administered in compliance with state and federal regulations.

Finally, use of MMC requires that the physician's staff be familiar with USP <800>, which covers responsibilities for all personnel handling hazardous drugs, including procedures for disposal and documentation [71]. California has already adopted the USP <800> standards.

Preparing for USP <800>: A resource toolkit

- Occupational Safety and Health Administration. Safety and Health Topics. Hazardous Drugs. www.osha.gov/SLTC/hazardousdrugs/index.html (accessed August 13, 2018).
- Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html (Accessed August 13, 2018).
- The *USP Compounding Compendium 2017*, which includes USP <800>. www.usp.org/store/products/usp-compounding-compendium. (There is a cost involved.)
- USP <800> "Frequently Asked Questions." www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings.
- A USP <800> updates newsletter. www.usp.org/HQS-Signup-Form. (Available upon request).
- National Institute for Occupational Safety and Health. NIOSH alert: preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. www.cdc.gov/niosh/docs/2004-165/. (Accessed August 13, 2018).
- The *NIOSH List of Antineoplastic and Other Hazardous Drugs in Health Care Settings*, 2016. www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf. (Accessed August 13, 2018).
- NIOSH Safety and Health Topics: Hazardous Drug Exposures in Healthcare: Antineoplastic Agents. www.cdc.gov/niosh/topics/hazdrug/antineoplastic.html. (Accessed August 13, 2018).
- NIOSH Safety and Health Topics: Occupational exposure to antineoplastic agents and other hazardous drugs: Effects of occupational exposure. www.cdc.gov/niosh/topics/hazdrug/effects.html. (Accessed August 13, 2018).
- Pharmaceutical compounding—sterile preparations (general information chapter 797). In: The United States pharmacopeia, 39th rev., and the national formulary, 34th ed. Rockville, MD: United States Pharmacopeial Convention; 2016:626-70.
- American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: *Am J Health-Syst Pharm*. 2006; 63:1172-93.

A Question and answer for real-world scenarios

A glaucoma specialist wishes to start using MMC for subconjunctival MIGS procedures. As the surgeon is establishing his operating schedule, the pharmacist at the institution does not think the institution will be able to supply MMC because of the USP <797> and <800> standards. The pharmacist mentions that the institution does not have the compounding, storage, handling, and disposal procedures in place to stock MMC. As an antineoplastic injectable, MMC is required to be stored in a negative pressure room. The pharmacist also notes employees need to be competent to handle and dispose of in the appropriate hazardous drug waste containers. This was reviewed by the pharmacist's Pharmacy and Therapeutics Committee, which previously decided the volume of use was too low to justify implementing all the requirements USP <800> will require by adding MMC to its offerings. The pharmacist also wonders if this something the group will need to revisit to be able to provide for their ophthalmologists.

1. Are there any options for the ophthalmologist to recommend to the pharmacy staff so they can procure MMC?

The ophthalmologist could recommend the pharmacy staff obtain Mitosol (mitomycin for solution) 0.2 mg/vial Kit for Ophthalmic Use or compounded MMC, and this may relieve many of their concerns of storage and reconstitution. Mitosol is the only FDA-approved ophthalmic formulation of MMC. The kit contains a closed-system transfer device (CSTD) and sponge tray enabling the safe reconstitution and transfer of MMC. *Mitosol may or may not be compliant according to updated guidelines and/or state regulations; individual institutions should ascertain if they are compliant with new regulations.*

Compounded MMC offers a prescribed concentration of MMC that is ready for administration. This is especially true since many ophthalmic surgeons are now administering MMC subconjunctivally rather than applying local sponges. Compounded MMC does not require vial storage, reconstitution, and does not raise concerns around an aseptically prepared sterile preparation. These products often can be obtained from a registered compounding pharmacy that prepares sterile products. (www.achc.org; this site allows for searching of a sterile product's compounding pharmacy at a nearby location; see paper)

2. What about the concerns expressed by the pharmacy personnel regarding proper disposal of the MMC?

The concerns of healthcare personnel (HCP) exposure and requirements for proper disposal of a hazardous drug are very relevant.

The Mitosol product insert states that it is reconstituted using a CSTD device and sponge tray enabling the safe reconstitution and transfer of MMC. The manufacturer also notes that "PPE must be worn, removed, and disposed of in an approved hazardous waste container at the site of drug administration [7]".

Of note, compounded MMC would also require proper disposal after use as described above.

Operating room and ambulatory surgery center staff must always be trained about proper disposal of any hazardous drug. HCPs will need to ascertain that proper equipment required for disposal of any contaminated articles that come in contact with MMC are available after discussion with their ambulatory care or hospital staff. Further information can be found in a publication from the American Society of Ophthalmic Nurses (ASORN), entitled "Mitomycin C: Indications for Use and Safe Practice in Ophthalmology" (http://www.asorn.org/resources/mitomycinc_learning_module)

Occupational safety resides under Occupational Safety and Health Administration (OSHA), and sites where employee personnel have identified hazards must educate, protect and monitor their staff. OSHA has a chapter

in the safety manual devoted to hazardous safety and the Department of Labor is very aware of the hazards and what needs to be in place to protect staff. Disposal resides with the Environmental Protection Agency, which clearly defines how hazardous substances must properly be disposed. Some states have stricter regulations governing disposal.

3. Will the future procurement of compounded MMC be a problem with these new guidelines and the ones coming into use soon?

Two new guidance documents were published in January 2018* whose purpose is to prevent pharmacies and outsourcers from making, compounding, and manufacturing commercially available FDA reviewed products. Responsibility and burden for drug quality, drug integrity, and compliance with regulatory standards resides with physician offices, ambulatory surgical centers, and hospital pharmacies directly ordering compounded MMC.

The FDA has full oversight over compounding manufacturers registered as 503B and is relying on state boards of pharmacy to manage oversight of 503A compounding pharmacies providing patient specific compounded drugs.

The FDA has stated very clearly that “compounded drugs can serve an important need, but they can also pose a higher risk to patients than FDA-approved drugs.” In addition, the FDA states “if a commercially available, FDA-vetted product is used, it protects from compounding deficiencies which resides on FDA to assure the pharma industry is compliant.” Clearly defined within both documents is the definition of “essentially copies.” The “FDA intends to consider a compounded drug product to be identical or nearly identical to an approved drug (essentially a copy) if the compounded drug product and the FDA-approved drug have the same: active ingredient(s), route of administration, dosage form, dosage strength, and excipients.

Based upon the definition above, the use of a different concentration and/or route of administration (sponge vs. subconjunctival) should allow for use of compounded MMC for subconjunctival injection.

* In January 2018, the FDA published two guidance documents entitled: “Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry” and “Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry.”

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